Remarks

In response to the Restriction Requirement dated October 2, 2003, applicants elected Group I, claims 1-5 and 20-26, and the species of SEQ ID NO:1. Claim 2 was cancelled. Claims 1, 3, 5, 20 and 25 were amended to reflect the election of Group I (antisense) and SEQ ID NO:1. In the present amendment, claim 22 is cancelled, and claims 1, 3, 5, 20, 23 and 25 are amended as discussed below. No new matter is added.

Applicants acknowledge the Examiner's statement that SEQ ID NO:1, elected in response to the restriction requirement filed on February 14, 2003, is not a species, but a distinct invention. (Page 2, lines 15-17.) In reference to the alleged burden of searching more than one sequence per application, applicants submit that the disclosed SEQ ID NO:1, 3 and 5 are all encompassed by disclosed SEQ ID NO:9, which is a polynucleotide sequence encoding KIAA0175. It is submitted that a search of each of SEQ ID NO:1, 3 and 5 would not be unreasonable. Search parameters can be defined such that oligonucleotides and short polynucleotides having homology to SEQ ID NO:9 would be identified. Applicants therefore disagree with the concept that SEQ ID NO:1, 3 and 5 are "chemically distinct," (Office Action, page 2, lines 3-6) as they are searchable together as part of SEQ ID NO:9. Furthermore, Applicants are presently prosecuting other unrelated applications claiming multiple antisense oligonucleotides, in which several antisense molecules are under examination in one application. This indicates an inconsistent policy with respect to searching short oligonucleotide sequences.

Finally, applicants note that the Examiner has referred to SEQ ID NO:1, 3 and 5 throughout the Office Action (page 5, lines 5 and 6; page 7, line 19; page 8, line 8, etc.), suggesting that the Examiner is considering these molecules together. Applicants further note that no prior art has been cited against SEQ ID NO:1. For all the foregoing reasons, Applicants reiterate their request to have SEQ ID NO:3 and 5 also examined in this application. By including all three sequences in the discussions in the Office Action, the Examiner indicates that the 35 U.S.C. § 112 issues would be the same, further indicating no undue burden.

Formalities

Priority. Applicants appreciate the indication that the priority to application Serial No. 60/208, 435 under 35 U.S.C. § 119(e) has been acknowledged.

Information Disclosure Statement. Applicants note the Examiner's comments.

Drawings. A corrected drawing (Figure 1) is filed herewith.

Claim Objections. The objection to claims 20-26 is addressed by amendment herein.

Rejections

Claims 1, 3-5 and 20-26 were rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of written description in the specification. Applicants traverse this rejection on the grounds that by providing the sequence of KIAA0175 polynucleotide (SEQ ID NO:9) they have provided written description for oligonucleotides capable of hybridizing with SEQ ID NO:9. This is not a situation wherein one of skill must provide missing information; on the contrary, all the possible antisense oligonucleotides are contained within the disclosed sequence and are therefore written in the application.

This situation is distinguishable from the written description issues described by the Court of Appeals for the Federal Circuit in The Regents of the University of California vs. Eli Lilly and Company, 119 F.3d 1559 (C.A.F.C. 1997) wherein the Court held that the name "cDNA" is not itself written description of DNA, in the absence of sequence information indicating which nucleotides constitute human cDNA for insulin. In the present case, the sequence information is provided in SEQ ID NO:9. Reconsideration and withdrawal of this rejection are respectfully requested.

Claims 20-26 were rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of written description. Claim 20 as amended recites that at least one of the KIAA075 inhibitors is an antisense molecule of SEQ ID NO:1. To the extent that the claim scope includes one or more inhibitors, any such inhibitor known in the art is suitable, and is not intended to be limited to the enumerated inhibitors. For example, by specifying that one portion of the composition is an antisense molecule, such as SEQ ID NO:1, applicants have identified the material that one of skill would not be able to ascertain from the prior art, alone or in combination with inhibitors of claim 26. Reconsideration and withdrawal of this rejection are respectfully requested.

Claims 1, 3-5 and 20-26 were rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. The Examiner cited the Ex parte Forman (230 U.S.P.Q. 546 (Bd. Pat. App. & Inter. 1986)) and In re Wands (8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988)), factors in support of this ground of rejection.

A specification is presumed to be enabling and the U.S. Patent and Trademark Office (PTO) has the burden of establishing a *prima facie* case of lack of enablement. See, In re Angstadt, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976); In re Marzocchi, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971). To make a *prima facie* case of lack of enablement, the PTO must come forward with reasons, supported by the record as a whole, showing why the specification fails to enable one of ordinary skill in the art to make and use the claimed invention. In re Angstadt, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). The mere fact that some experimentation is necessary does not negate enablement as long as undue experimentation is not required. See M.P.E.P. § 608.01(p).

The burden is on the PTO to establish that experimentation would be undue, Angstadt, 190 U.S.P.Q. at 219, taking into consideration the eight factors that are to be considered in determining whether a disclosure requires undue experimentation. In re Wands, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Applicants submit that the amount of experimentation which may be required to practice the present invention does not rise to the level of being undue experimentation, as defined by the Court in Wands.

Like the production of monoclonal antibodies, the identification or production of a polynucleotide having antisense activity may require some experimentation, but if viewed in the light of Wands, this experimentation, and the possibility of encountering negative results along the path to the positive results, is not undue. Furthermore, the present applicants provide extensive guidance to allow one of ordinary skill in the art to obtain polynucleotides that are within the scope of the claims.

Analyzing the present claimed invention under the eight Wands factors, one of skill in the art would conclude that undue experimentation would not be required to practice the claimed invention.

1. *Quantity of experimentation necessary.* Applicants respectfully submit that one of ordinary skill in this art can routinely generate and use antisense oligonucleotides that are based upon the sequence of KIAA0175, provided herein as SEQ ID NO:9. The inventors have identified that antisense oligonucleotides capable of specifically binding to a KIAA0175 polynucleotide can affect biological processes that depend on KIAA0175 activity. The KIAA0175 protein product possesses an autophosphorylation activity that can be assayed, as described in the specification, Example 2 at pages 37-38. Thus, an objective test exists for measuring KIAA0175 activity. The specification also provides a method for detecting changes in KIAA0175 mRNA levels following administration of an antisense oligonucleotide, in Example 4, pages 39-40. The specification further discloses methods of measuring cell viability following transfection with an antisense oligonucleotide of the invention, and exposure of cells to irradiation or chemotherapeutic agents (Examples 8 and 9).

To determine if a polynucleotide falls within the scope of the claims, therefore, only the performance of cell transfection and assay procedures is required, with measurement of an objective outcome. These procedures are routine and would not have to be done repeatedly before a clear result was obtained. Because the inventors and the art provide means for the objective measurement of the biological effect of a polynucleotide falling within the claim scope, this factor is met. These biological effects include mRNA levels, and cell viability following exposure to a DNA-damaging agent or treatment.

The Wands court stated that an "experiment" was not simply the screening of a simple hybridoma, but instead was the entire attempt to make a monoclonal antibody against a particular antigen. This process included immunizing animals, fusing lymphocytes from the immunized animals to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas. (USPQ2d at 1406.)

By analogy, a single experiment in the present art could include obtaining or constructing an antisense oligonucleotide based on SEQ ID NO:9, conducting experiments as disclosed in Example 4, and measuring KIAA0175 MRNA levels. Another experiment could include transfection of cells with an antisense oligonucleotide of the invention, exposing the cell to an agent having use as a DNA-damaging agent, and measuring cell viability, as described in

Examples 8 and 9. Encountering negative results would not mean that undue experimentation is involved, according to Wands.

2. *Amount of direction or guidance provided.* The specification provides clear directions for performing the experimentation (including Examples 4, 8, and 9). Similarly, the Wands court found that the starting material was available to the public (as is the material used in the present application) and the patent at issue in Wands provided a detailed description of the methods, which included use of a commercially available kit. (8 USPQ 2d at 1404, 1405). The cell lines used in applicants' methods are commercially available, and the application describes the methods, at pages 39-47. The Examiner states that no nexus is provided for the use of antisense molecules of SEQ ID NO:1, 3 and 5 as a therapeutic composition in an organism. The claims do not recite a *use*. The claims recite antisense inhibitors of KIAA0175 mRNA. Such inhibition is measured, for example, by assaying the mRNA of cells exposed to the antisense molecules, such as described in Example 4. The claims recite compositions, not methods.

3. *Presence of absence of working examples.* The specification describes transfection of HT1080 cells using a claimed polynucleotide of the invention, specifically KIAA 0175 antisense oligonucleotides (pages 39-40). The experiment provides an example that is applicable to other claimed KIAA0175 anti-sense oligonucleotides (test polynucleotides), which would be used to transfect the HT 1080 cells. The inhibition of KIAA0175 mRNA would signal that the test polynucleotide is within the scope of the claims. The specification also describes measuring cell viability in cells transfected with an antisense molecule of the invention, and exposing the cells to a known DNA-damaging agent or treatment (pages 45-47).

4. *Nature of the invention.* KIAA0175 is the name given to a protein having homology to yeast Rad53. In yeast, Rad53 is essential in the control of entry of cells into the S phase of the cell cycle, which is the phase of DNA synthesis. Rad53 is also phosphorylated and activated in response to DNA damage (specification at page 5, line 18 through page 6, line 3). Thus, KIAA0175 plays a role in DNA synthesis during the cell cycle, and in facilitating DNA repair after damage such as by irradiation and chemical agents. Applicants believed that inhibition of KIAA0175 could have implications in the ability of a cell to survive damage to its

DNA. As DNA damage is a goal of many therapies, such as γ-irradiation and chemotherapy for cancer, applicants sought a means for inhibiting KIAA0175. One such means is provided by the antisense oligonucleotides and methods disclosed in the application.

To fulfill its biological role, KIAA0175 protein expression increases following exposure of cells to DNA-damaging agents such as γ-irradiation or hydroxyurea (specification at page 6, lines 14-16). By inhibiting KIAA0175 gene expression, it is possible to abrogate the cell cycle arrest that is associated with such treatment, abolishing the damage repair, and leaving cells *vulnerable* to the cytotoxicity of these therapeutic DNA damaging agents (specification at page 7, lines 15-18). Antisense inhibitors of KIAA0175 have numerous utilities, including *in vitro* inhibition of KIAA0175 protein expression in cells, thereby allowing one of skill to test radiation and chemotherapeutic agents for their cytotoxic effects in the cells with and without functional KIAA0175. Such methods are disclosed, for example, at page 23, line 9 through page 24, line 4.

Applicants respectfully submit that the Examiner has inappropriately focused on gene therapy as the utility of the invention as claimed. Applicants strongly disagree with this limited characterization of the invention. On the contrary, the invention is useful in testing radiation and chemotherapeutic agents for their effect on cells *in vitro*. This aspect of the invention must be taken into account when evaluating enablement under the Wands factors. The invention relates to human polynucleotides. Methods of synthesizing, isolating, mutating, manipulating, transfecting, and expressing polynucleotide are the basis for the biotechnology industry. The nature of the invention is such that it is well-known to those of ordinary skill in the art. The court in Wands stated that the nature of monoclonal antibody technology is such that it involves screening (in that case, hybridomas). The present invention provides antisense molecules, contrary to the Examiner's statements at page 9, lines 8-12.

Applicants earnestly submit that the nature of the invention relates to the ability of KIAA0175 inhibitors, in this instance, antisense oligonucleotides, to sensitize cells to DNA-damaging agents such as γ-irradiation, hydroxyurea, and other potentially useful chemotherapeutic agents. Such an effect can be tested as clearly described in the specification, for example at pages 44-45 (Examples 8 and 9). Example 8 clearly describes the transfection of

HCT116 cells with KIAA0175 antisense molecules or control molecules. The cells are then treated with the DNA-damaging method or composition of choice, such as γ-irradiation or hydroxyurea. Viability is assessed at specified days after treatment, and the extent of viability correlates with the ability of the antisense treatment to sensitize the cells to the DNA-damaging agent. The ability of KIAA0175 antisense oligonucleotides to sensitize cells to chemotherapeutic agents, radiation, or other putative DNA-damaging agents can be assessed in this manner *in vitro* (Examples 8 and 9). Such results can then be used to guide decisions about treatment of an organism.

For the foregoing reasons, applicants strenuously urge that the nature of the invention is much broader than the limited scope suggested by the Examiner, namely, gene therapy. Viewing the nature of the invention in the light described in this section, it is indisputable that undue experimentation is not required to practice the invention and to identify antisense oligonucleotides within the scope of the claims.

5. *The state of the prior art.* The state of the art is such that, similar to the art discussed in Wands, those of skill expect to conduct experimentation to achieve positive results. The new information that the inventors bring to the field relates to the identity of the gene to be inhibited by the antisense molecules as claimed, and not to antisense technology and procedures generally. The prior art provides the methods and materials needed to apply the methods of factor (4) above to this group of oligonucleotides, specifically KIAA0175 antisense oligonucleotides. The Wands court found that "all the methods needed to practice the invention were well-known." (8 USPQ 2d at 1406). Similarly, the methods of transfecting cells, expressing mRNA, measuring mRNA levels, and assessing cell vitality are well known, as evidenced by the specification and by the references cited by the Examiner. The Examiner asserts that the state of the art for gene therapy is the standard to which the present invention applies. Applicants disagree, for reasons discussed in paragraph (4) above. The alleged problems with gene therapy include, according to the Examiner, the vectors used for gene therapy (page 10, lines 16-17), for example. These broader problems are not addressed by, nor are they intended to be addressed by, the current invention.

6. *The relative skill of those in the art.* Those of skill in this art are highly skilled and would be competent at designing and performing, or directing the performance of, the procedures of factors (4) and (5) above. The Wands court found that the level of skill in the monoclonal antibody was high at the time the application was filed, but, importantly, the court also found that *development of skill* in performing specific experiments relevant to the art did not preclude enablement. Specifically, the court stated that initial failures occurred as the inventors learned to fuse cells, and "[o]nce they became skilled in the art, they invariably obtained numerous hybridomas ..." that met the claim limitations. (8 USPQ 2d at 1406). By analogy, it would not defeat enablement for one of skill in the art of antisense transfection and expression to learn and become proficient in techniques for practicing the present invention. Notwithstanding the Examiner's statements at page 11, lines 14-18, it is not the responsibility of the present inventors to teach those of skill how to overcome the alleged deficiencies of gene therapy in general.

7. *The predictability or unpredictability of the art.* One of skill, being acquainted with the methods described in the application, would predict that when a KIAA0175 antisense molecule was transfected into HT1080 cells, the inhibitory effect on KIAA0175 mRNA would be objectively detectable. The person of skill, testing other polynucleotides as claimed, would predict that the outcome would reflect the ability of the test polynucleotide to hybridize with KIAA0175 polynucleotide in the cell, and that this would be the primary variable affecting the results. Those of skill are prepared to use appropriate control experiments to limit the effect of the variability of experimental conditions on the results.

In Wands, the Court noted that the cell fusion technique was well known to those of ordinary skill in the art, and that there was no indication that the fusion step would be more difficult or unreliable for the antigen in question (HBsAg) than for other antigens. Transfection of a cell and measuring the level of KIAA0175 mRNA is taught in the present specification, and the Examiner has provided no evidence that the transfection step would be "more difficult or unreliable" (8 USPQ2d at 1406) than for other anti-sense molecules.

8. *The breadth of the claims.* Using materials and methods routinely available at the time of filing, one of skill can routinely identify or construct any nucleic aid

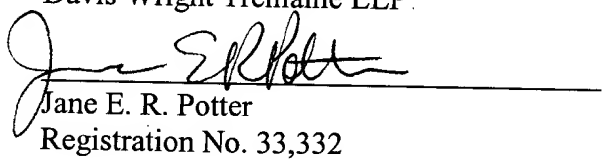
molecule meeting the limitations of the claims, and test it for activity as described for the previous factors.

In view of the foregoing remarks, applicants submit that the Examiner has not met his burden of making a *prima facie* showing that undue experimentation is required in order to practice the invention as claimed. The Examiner refers to "a tremendous amount" of experimentation (page 12, line 13) but amount of experimentation does not make it undue experimentation: That is the clear message of Wands. Reconsideration and withdrawal of this rejection are respectfully requested.

Claim 5 was rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness, by its dependence from claim 2. Claim 5 as amended is independent, thereby obviating this ground of rejection.

Withdrawal of the rejections and allowance of the pending claims is earnestly requested.

Respectfully submitted,
Bin Wu et al.
Davis Wright Tremaine LLP



Jane E. R. Potter
Registration No. 33,332

2600 Century Square
1501 Fourth Avenue
Seattle, WA 98101-1688
Phone: (206) 622-7650
Fax: (206) 628-7699